

### **REMARKS**

Applicant respectfully requests reconsideration. Claims 30-41, 70-74 and 80-83 were previously pending in this application. No amendments have been made. As a result, claims 30-41, 70-74 and 80-83 remain pending for examination. No new matter has been added.

### **Rejections Under 35 U.S.C. § 102**

1. The Examiner has rejected claims 30-36, 39, 74, 80, and 83 under 35 U.S.C. § 102(e) as being anticipated by Graham (US Patent 6,573,099). Applicant respectfully requests traverses the rejection.

The Examiner cites claim 4 of Graham as allegedly disclosing Applicant's invention, citing a long passage from the claim. (Office Action at page 4.) Applicant respectfully submits that this claim clearly shows the difference between the instant claimed invention and the expression vector described in Graham. Specifically, claim 4 of Graham states that the genetic construct comprises "at least two copies of a structural gene sequence." (emphasis added) In the constructs described in Graham "...each copy of said structural gene sequence is separately placed under the control of a promoter...." (Graham, claim 4, emphasis added.)

The claimed invention includes an "expression vector that comprises promoters flanking a DNA sequence". In the claimed invention, there is only one structural gene sequence, i.e., one copy of the gene, which is flanked by the promoters such that it is then operatively placed in a sense orientation under the control of a first promoter and (automatically) in an antisense orientation of a second promoter.

Graham neither shows nor describes that one copy of a gene sequence is placed between two promoters and that this one copy of the gene sequence is a template for both the sense and antisense transcript.

On page 5 of the Office Action, the Examiner states that “Graham teaches that one can use two identical promoters or preferably use two difference promoter sequences,” citing to col. 12, lines 42-50 of Graham. Applicant respectfully submits that this passage pertains to a specific embodiment in which a “multiple structural gene unit” is used, and in which each structural gene of the multiple gene unit is placed under the control of a separate promoter sequence (see col. 12, lines 42-44). Graham teaches that in *this embodiment*, the promoters preferably are different.

In summary, Graham does not describe all of the elements of the instantly claimed invention and therefore does not anticipate the claimed invention. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection made under 35 U.S.C. § 102(e).

### **Rejections Under 35 U.S.C. § 103**

1. The Examiner has rejected claims 30-41, 70-74, and 80-83 under 35 U.S.C. § 103(a) as being unpatentable over Timmons et al. (*East Coast Worm Meeting*, abstract 180; “Timmons”) in view of McAllister et al. (US Patent 5,017,488, “McAllister”), Conkling et al. (US Patent 5,459,252), and Talkad et al. (J. Bacteriol. 135:528-541, 1978). Applicant respectfully traverses the rejection.

#### **The cited combination of references does not provide all of the elements of the claimed invention**

McAllister provides plasmids that contain an improved T3 promoter in combination with either a SP6 promoter (plasmid pJFK15) or a T7 promoter (plasmid pJFK16). The T3/SP6 or T3/T7 promoter pairs flank a polylinker segment into which a DNA fragment of interest is placed. As described by McAllister, this DNA fragment is “to be transcribed” (col. 2, lines 22-23) to “synthesize RNA probes of high sensitivity” (col. 3, lines 44-46). The purpose of these vectors is further emphasized in claim 7: “...the recombinant DNA vector being capable of transcription of DNA to produce RNA strands **complementary to either one** of the strands of the inserted DNA

sequence when there is supplied to the vector a phage promoter-specific polymerase...” (emphasis added). Similarly in claim 13, McAllister emphasizes the use of the vectors: “A kit for genetic applications especially for transcription of DNA to synthesize RNA transcripts complementary to either strand of a DNA sequence...”(emphasis added). At the time of filing of the application, McAllister would have been read by the skilled person as teaching a dual promoter vector for synthesizing either strand of a DNA insert, but not both strands at one time.

In US 10/057,108, to which this application claims priority, Applicant submitted on December 22, 2009 a Declaration from Erwin Sablon, in which the use of vectors such as those described in McAllister were described. (A copy of this Declaration is provided herewith for the Examiner.) The specific reference discussed was a patent of Noren et al. (U.S. Patent No. 5,691,140), which described a multiple cloning site flanked by two phage RNA polymerase promoters positioned to express either strand of a DNA molecule inserted in the multiple cloning site. (See, Sablon Declaration at ¶7.) Similar to the McAllister patent, the Noren patent described using the appropriate phage RNA polymerase to generate either sense or antisense transcripts from the same vector. (See, Sablon Declaration at ¶8.) Paragraphs 9 and 10 of the Sablon Declaration describe how the plasmids described in Noren would be used to ensure that only one strand was transcribed, and that the plasmids clearly were not intended to simultaneously produce transcripts from both directions. The use of the bidirectional expression vectors described in US 10/057,108, for in vivo generation in *E. coli* of double stranded RNA was discussed in the Sablon Declaration at ¶11.

As in US 10/057,108, the vectors recited in the instant claims are used for producing double stranded RNA *in vivo*. Thus, McAllister fails to describe an element of the claimed invention, and none of the other cited references provide this missing element. Accordingly, the cited combination of references does not provide all of the elements of the claimed invention, and thus the cited combination of references does not render the claimed invention obvious.

Motivation to combine the cited references is lacking

Nor would the skilled person have been motivated to introduce the plasmid of McAllister into the organism of Timmons, or to modify the Timmons expression vector. The Examiner's stated motivation for doing so is contrary to the stated use provide in McAllister, e.g., to produce single stranded RNA probes. Thus the skilled person would not have used the expression plasmid of McAllister in the bacteria of Timmons. See paragraph 11 of the Sablon Declaration in support of the lack of motivation of the skilled person.

The cited combination of reference does not provide all of the elements of the claimed invention and does not provide motivation to combine the respective teachings of the cited references. Therefore, Applicant respectfully requests that the Examiner withdraw the rejection made under 35 U.S.C. § 103.

2. The Examiner has rejected claims 30-41, 70-74, and 80-83 under 35 U.S.C. § 103(a) as being unpatentable over Fire et al. (WO99/32619; "Fire PCT application"), in view of Graham (US Patent 6,573,099), Ely et al. (US Patent 5,837,848) and Talkad et al. (J. Bacteriol. 135:528-541, 1978). Applicant respectfully traverses the rejection.

The Fire PCT application is not prior art to the claimed invention

The Examiner asserts that the Fire provisional application (US 60/068,562) supports the teachings of the Fire PCT application, which are asserted to include inhibiting "target gene expression in a cell with an expression vector that synthesizes and produces two separate complementary strands and form[ing] an RNA duplex inside the cell." (Office Action at page 8.) The Examiner asserts that claims 1, 14, 16, 20 and pages 11 and 13 of the Fire provisional application adequately supports these alleged teachings, which Applicant takes to mean that the Fire provisional application provides an adequate written description under 35 U.S.C. § 112, first paragraph. Applicant respectfully disagrees. There is nothing in the Fire provisional application that describes using a bacterium containing a plasmid that directs the expression of double stranded

RNA in an organism that takes up the bacterium. None of the claims or specification pages cited by the Examiner describe such concepts.

The Fire provisional application, at the indicated locations, does not provide an adequate written description. Claim 1 recites introducing double stranded RNA into a cell to inhibit expression of a gene. Claim 14 recites that RNA has two separate complementary strands. Claim 16 recites synthesis of the two complementary strands and initiation of RNA duplex formation inside the cell. Claim 20 recites that an expression vector in a cell produces the RNA. Each of claims 14, 16 and 20 depend from claims 1-12, and thus these three claims fail to teach their individual recitations in combination with anything other than the recitations of claims 1-12. For example, the recitations of claims 16 and 20 are not combined – there is no teaching that the expression vector of claim 20 can be used in the synthesis step recited in claim 16. In fact, based on the knowledge in the art at that time, as evidenced by the Sablon Declaration that is described above, the skilled person would not have even attempted to make this combination.

On page 11, the only recitation of the use of expression vectors is that “[t]he use and construction of an expression vector are known in the art”, citing to several references from 1990 and 1991, and a 1997 PCT published application. The 1990 and 1991 references are standard laboratory manuals. The 1997 PCT published application is directed to methods of transforming plant tissue using a bacterium such as *Agrobacterium tumefaciens*. The plasmids described on pages 4-5 of this PCT application contain different genes (one gene of interest and one antibiotic resistance gene for selection) driven by different promoters. None of the plasmids described in this PCT application are used to produce RNA corresponding to both strands of a gene sequence. Therefore none of the references cited on page 11 of the Fire provisional application provide any description of a plasmid that could be used in producing RNA corresponding to both strands of a gene for the production of double stranded RNA.

On page 13, following a lengthy list of tumor types, the Fire provisional application states, *in reference to certain prior art references*, that “[i]ntroduction of RNA into cells can be used in

certain biological systems to interfere with function of an endogenous gene.” (emphasis added) No further description of the method of introducing the RNA, or any other aspect of the invention later claimed in the Fire PCT application, is provided. Thus the recitation on page 13 of the Fire provisional application does not contribute to an adequate written description of that which the Examiner alleges to be “target gene expression in a cell with an expression vector that synthesizes and produces two separate complementary strands and form[ing] an RNA duplex inside the cell.” (Office Action at page 8.)

Therefore, Applicant respectfully submits that the Fire provisional application does not provide an adequate written description of the recitation that the Examiner alleges for the Fire PCT application. Accordingly, the Fire PCT application does not have an effective priority date that is prior to the effective filing date of Applicant. As such, the Fire PCT application is not prior art to the instant claims, and therefore the rejection of the claims as obvious over this cited combination of references fails.

The cited combination of references does not provide all of the elements of the claimed invention

The Examiner also includes the Graham patent in the combination of references cited. As argued above in the section responding to the rejection of claims 30-36, 39, 74, 80, and 83 as anticipated by Graham, in the constructs described in Graham “...each copy of said structural gene sequence is separately placed under the control of a promoter...” (Graham, claim 4, emphasis added.) In contrast, in the claimed invention, there is only one structural gene sequence, i.e., one copy of the gene, which is flanked by the promoters such that it is then operatively placed in a sense orientation under the control of a first promoter and (automatically) in an antisense orientation of a second promoter.

Thus Applicant respectfully submits that Graham does not provide an element of the claimed invention. As such, the rejection of the claims as obvious fails for the additional reason that the cited combination of references does not provide all of the elements of the claimed invention.

**Motivation to combine the cited references is lacking**

Finally, the Examiner states on page 10 of the Office Action that motivation exists to combine the cited references because the expression vectors of Graham and Fire are “art-recognized equivalents”. It clearly is not the case that the expression vectors of Graham and Fire are “art-recognized equivalents”, based on the citation in the Fire priority application of standard laboratory manuals for a description of expression vectors as compared to Graham, which provides expression vectors deemed by the USPTO to be novel and inventive over the prior art, including those vectors referenced in the Fire provisional application.

In summary, the Fire PCT application is not prior art to the claimed invention, and even if the Fire PCT application is considered prior art, the cited combination of references does not provide all of the elements of the claimed invention and does not provide motivation to combine the respective teachings of the cited references. Therefore, Applicant respectfully requests that the Examiner withdraw the rejection made under 35 U.S.C. § 103.

**Double Patenting**

1. Claims 30-40, 70-74, and 80-83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-11 of copending Application No. 11/522,307.

Applicant respectfully requests reconsideration. Because claims 8-11 of copending Application No. 11/522,307 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

2. Claims 30-40, 70-74, and 80-83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-25 of copending Application No. 11/666,017.

Applicant respectfully requests reconsideration. Because claims 24-25 of copending Application No. 11/666,017 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

3. Claims 30-40, 70-74, and 80-83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27-28 and 34-35 of copending Application No. 11/666,021.

Applicant respectfully requests reconsideration. Because claims 27-28 and 34-35 of copending Application No. 11/666,021 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

4. Claims 30-41, 70-74, 80 and 83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-39 of copending Application No. 12/055,607.

Applicant respectfully requests reconsideration. Because claims 34-39 of copending Application No. 12/055,607 are not at present considered allowable, Applicant defers addressing this rejection until a later date.



5. Claims 30-41, 70-74, 80 and 83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-10 and 12 of copending Application No. 12/087,537.

Applicant respectfully requests reconsideration. Because claims 6-10 and 12 of copending Application No. 12/087,537 are not at present considered allowable, Applicant defers addressing this rejection until a later date.

6. Claims 30-41, 70-74, 80 and 83 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-27 of US Patent 7,358,069.

Applicant respectfully requests reconsideration. Claims 26-27 of US Patent 7,358,069 recite a DNA construct that produces double stranded RNA comprising first and second promoters in opposite orientation and a first transcription terminator operably linked to the first promoter. The present claimed invention does not recite a terminator linked to a promoter. Thus the claims are patentably distinct and should not be subjected to an obviousness-type double patenting rejection over claims 26-27 of US Patent 7,358,069.

**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. D0590.70011US02 from which the undersigned is authorized to draw.

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